ME/ CFS

- Identifiable
- Treatable
- Fundable

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Volunteer Associate Professor, Dept. of Medicine, University of Miami

** CFIDS Association of America*

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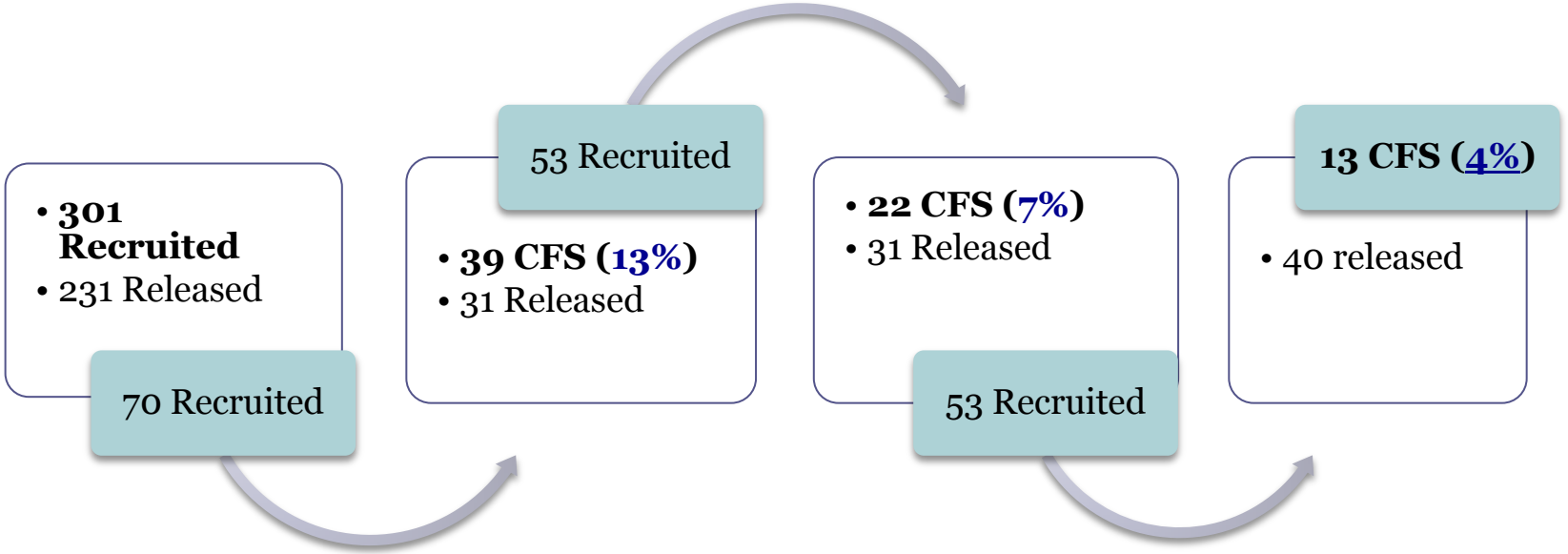
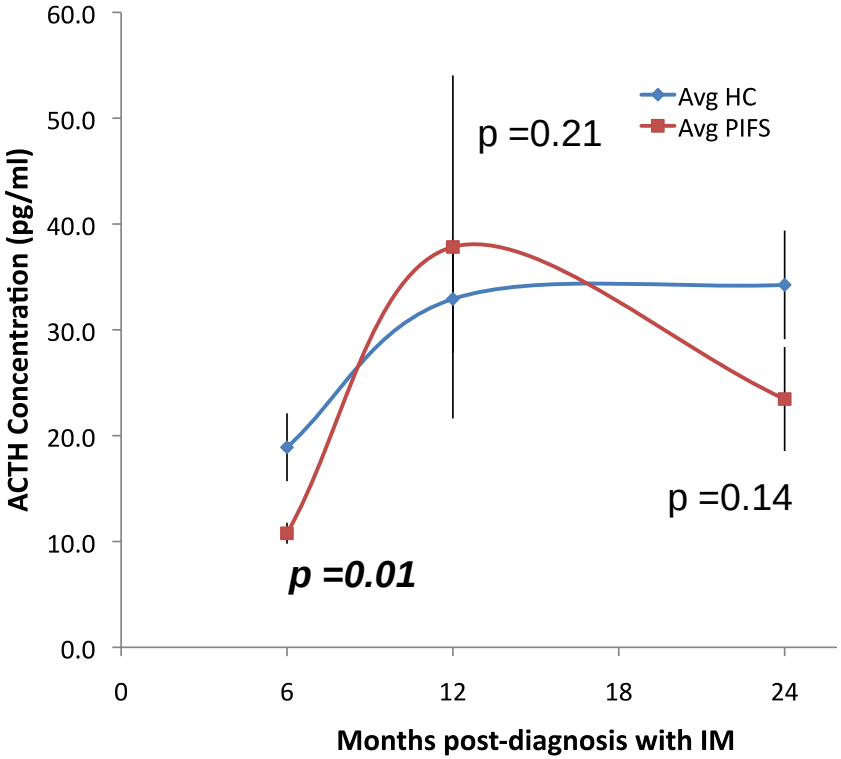
A prospective look at Mono

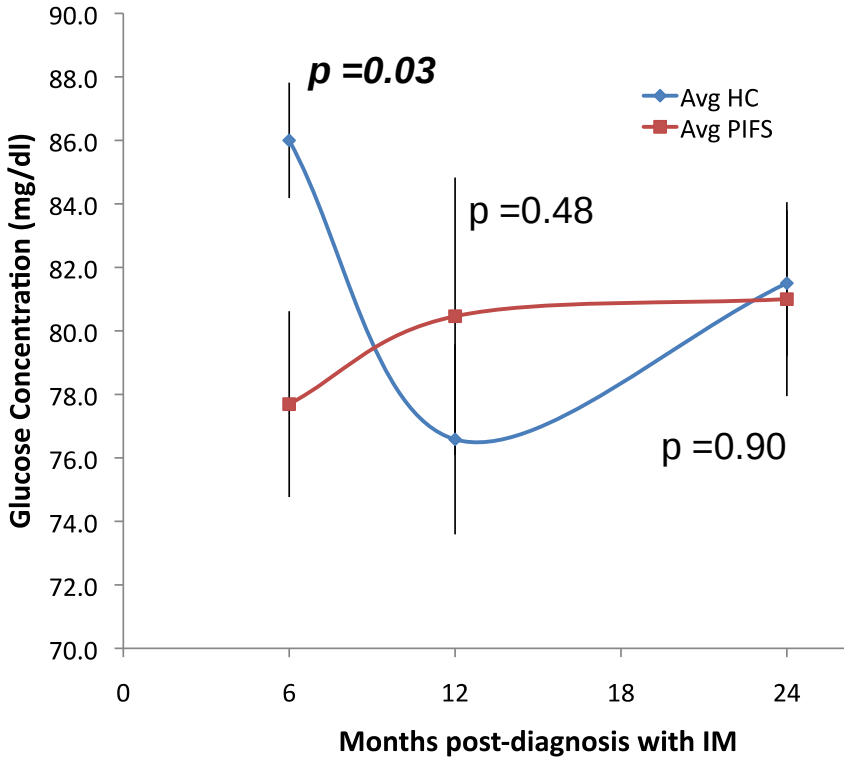


- *Fukuda (1994) exclusionary criteria*
- *Blinded case review Jason (2006) case definition*

Early screening opportunities

At 6 months post-IM diagnosis





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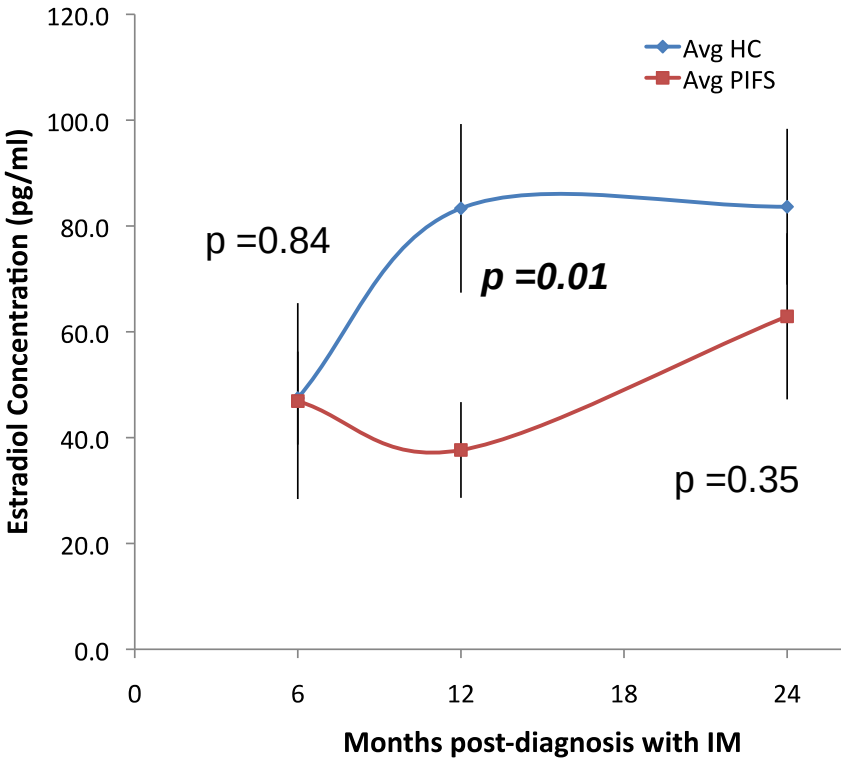
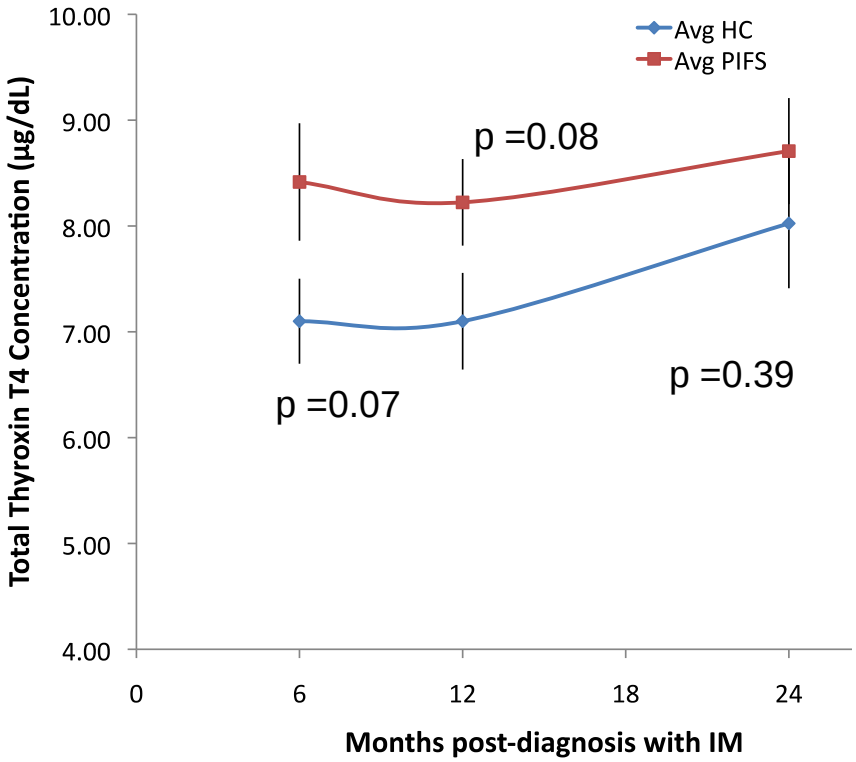
Early screening opportunities

At 12 months





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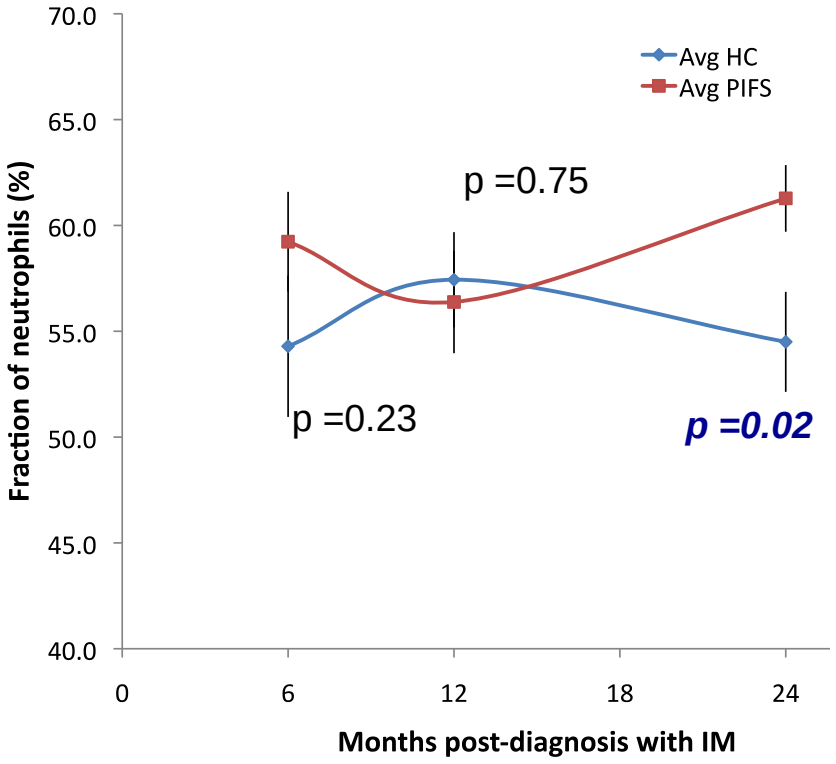
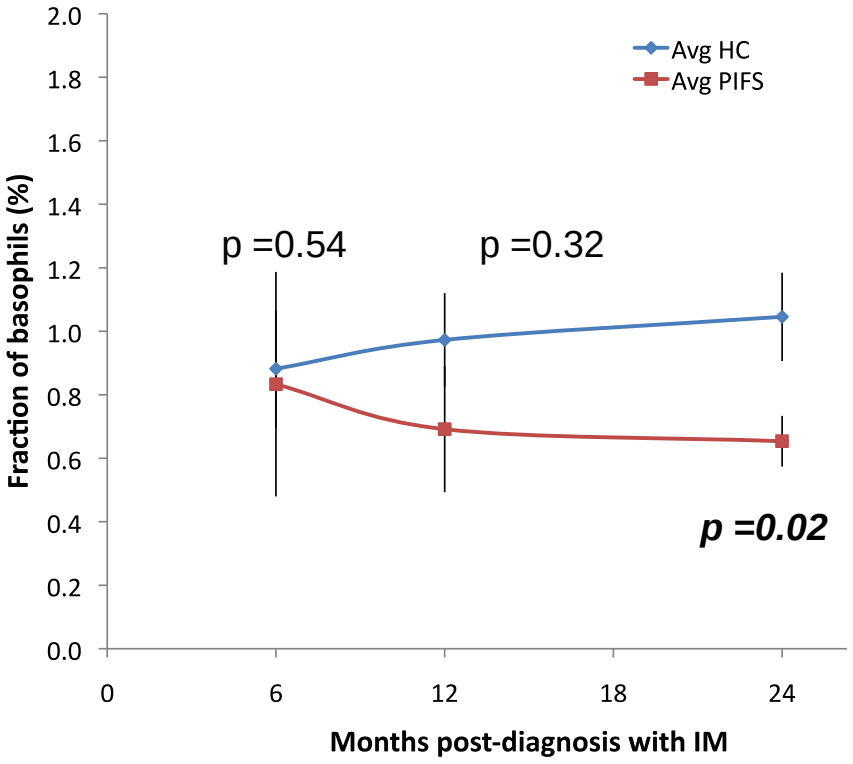
Early screening opportunities

At 24 months





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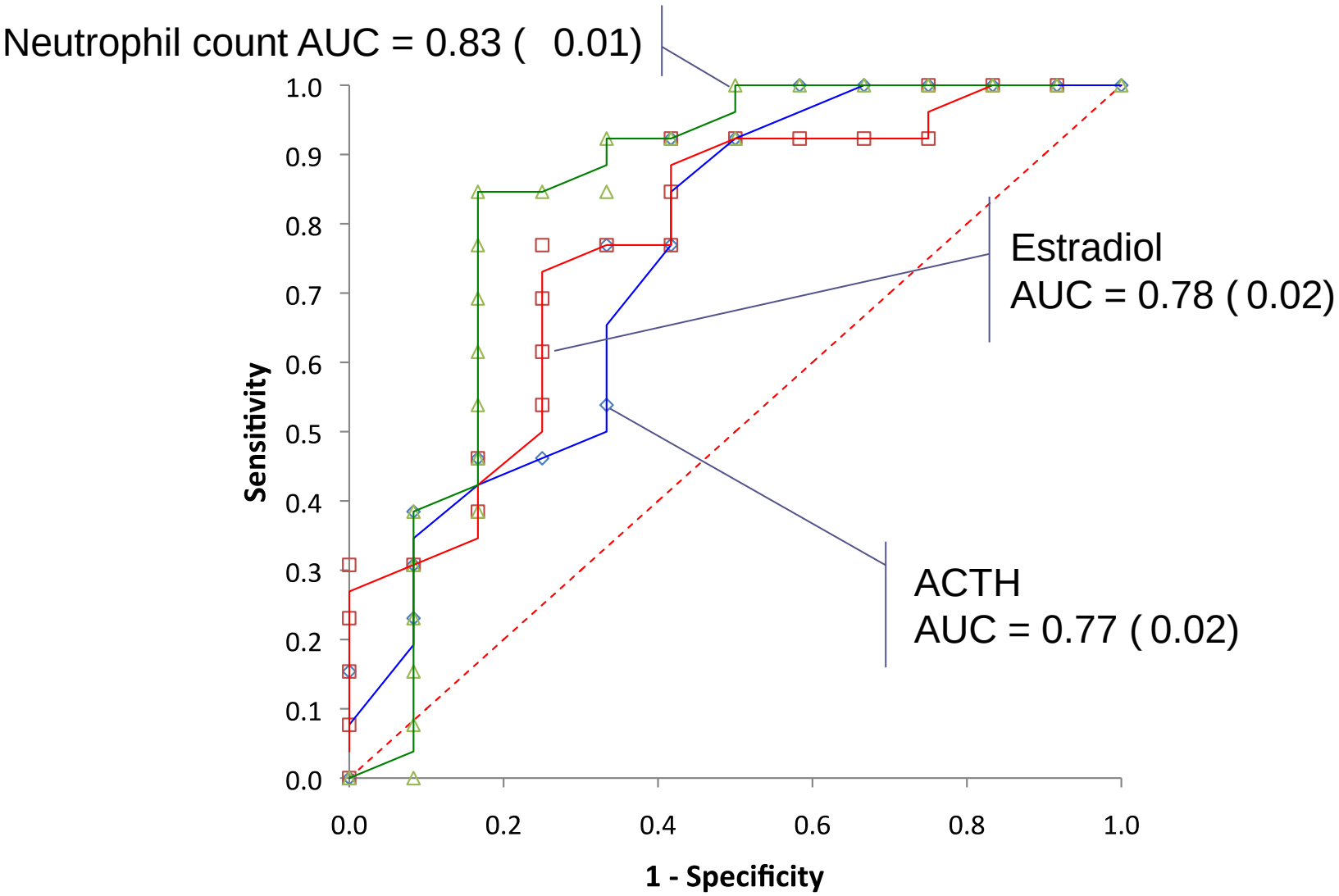
Simple markers?



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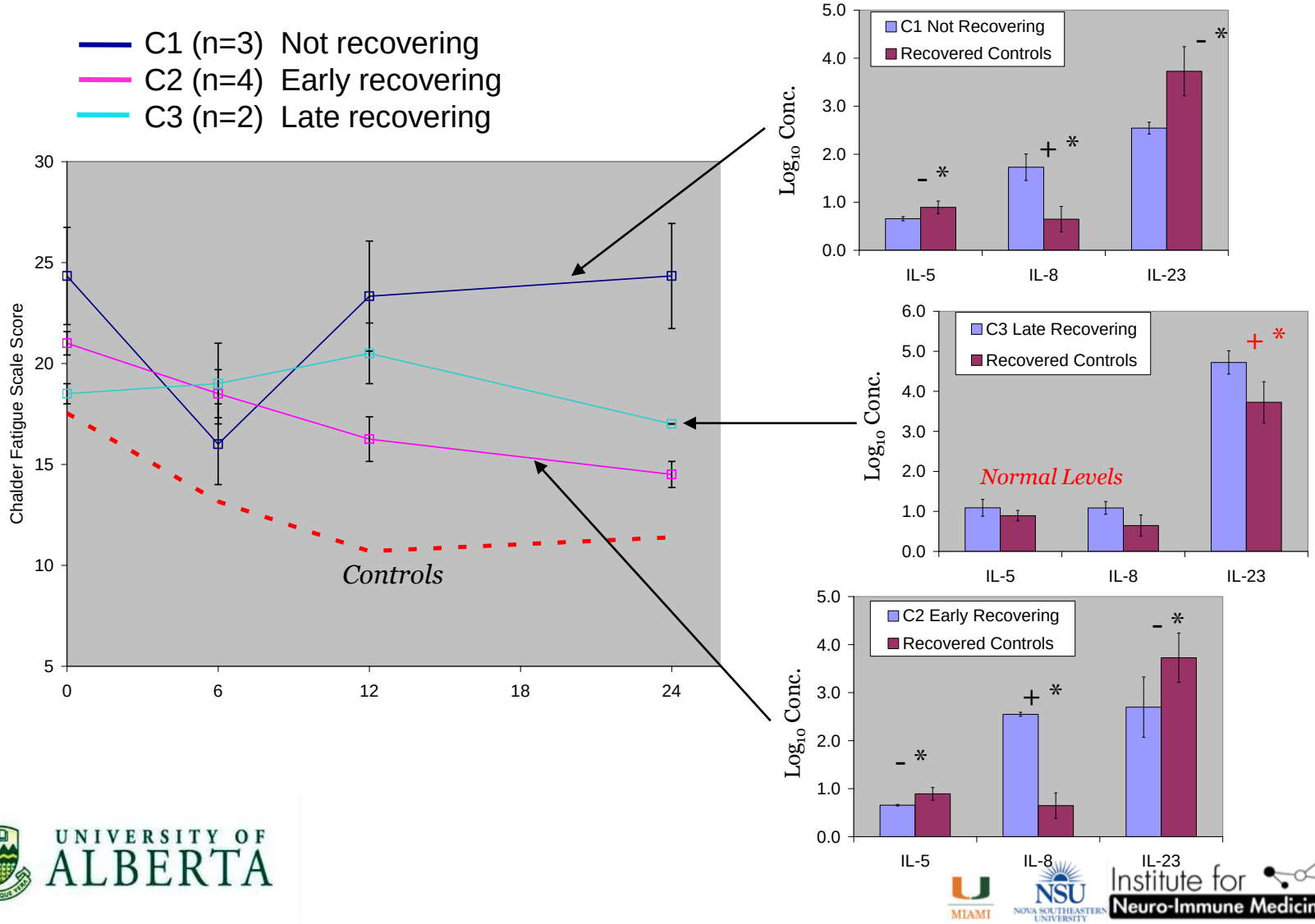
Shifting immune signals



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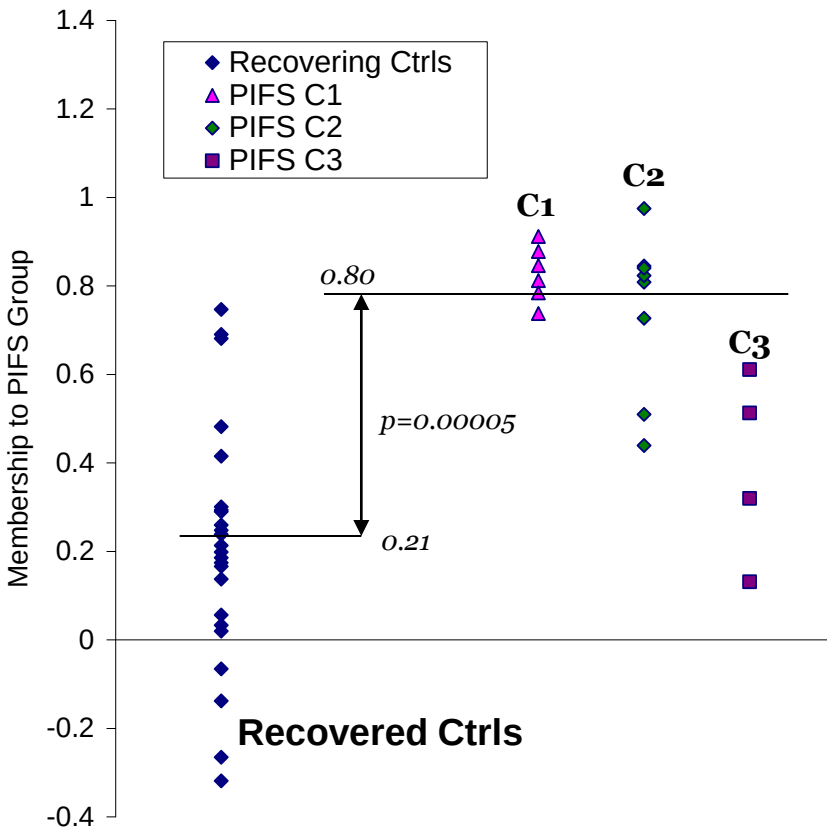
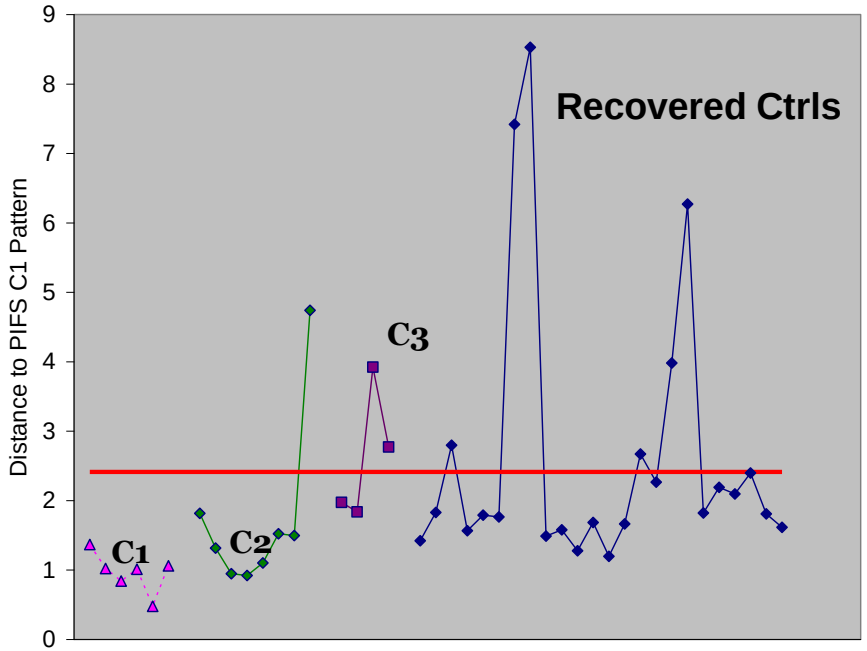
Adding context





IL-6, IFNg improve separation

C3 much more similar

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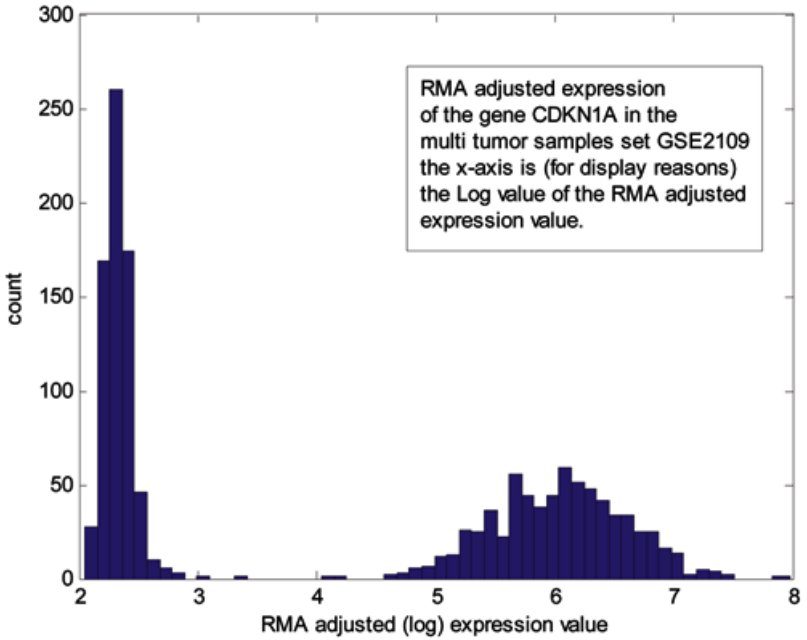
Digging deeper



- Map to Up/Down states for every gene *in each individual sample*
- Model expression values to a mixture of gamma distributions;

[1] Efroni S, Schaefer CF, Buetow KH.Identification of key processes underlying cancer phenotypes using biologic pathway analysis. PLoS One. 2007 May 9;2(5):e425.

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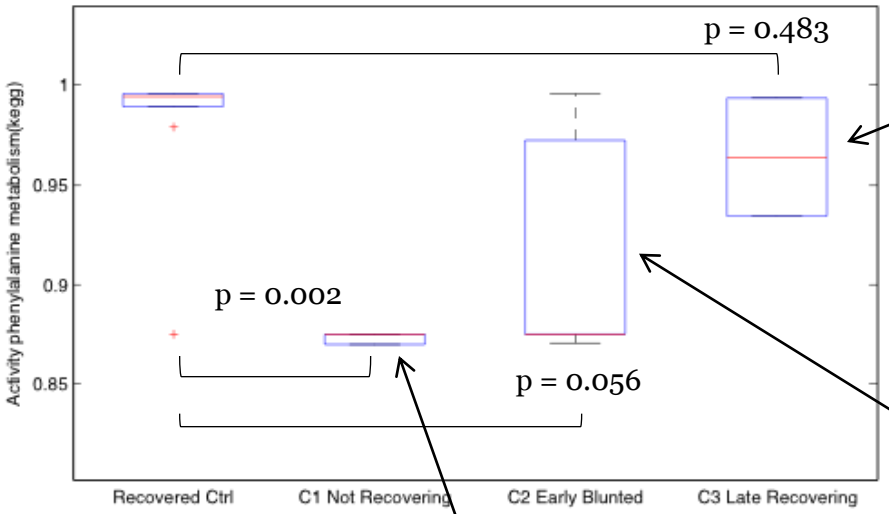
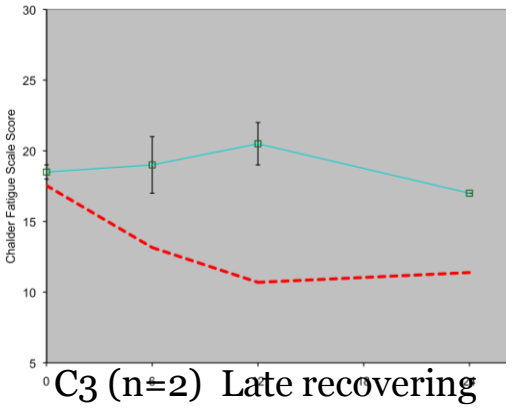
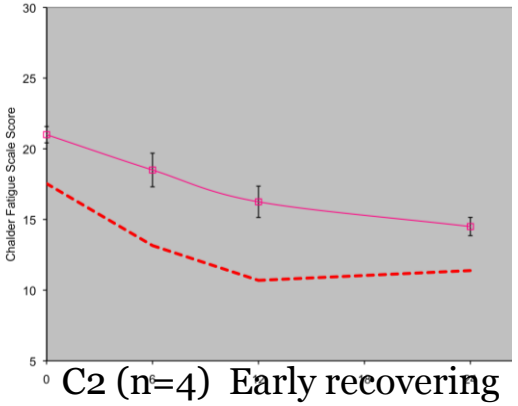
Pathway-level illness course

Phenylalanine metabolism

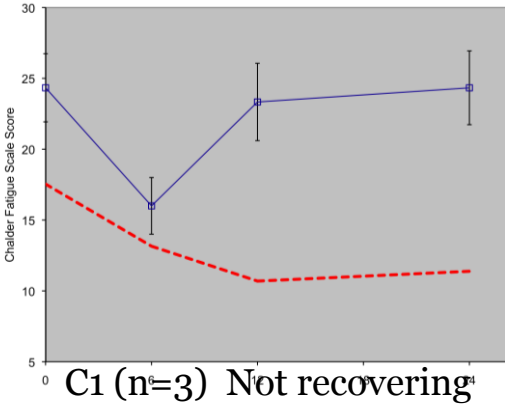




C3 (n=2) Late recovering



C2 (n=4) Early recovering



C1 (n=3) Not recovering

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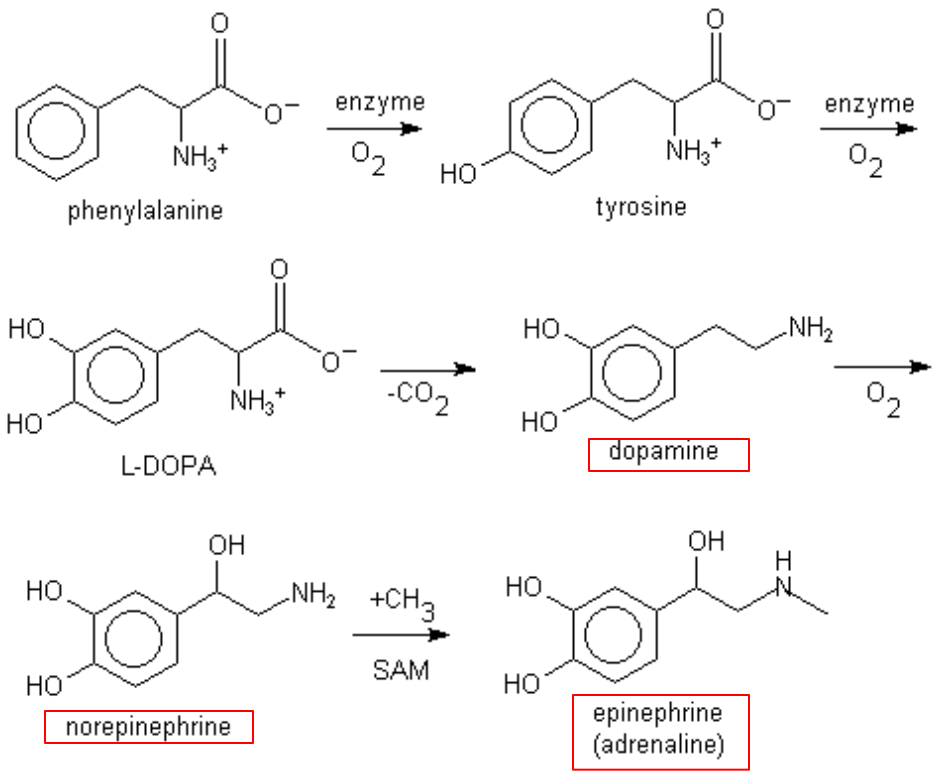
Phenylalanine up close

- Amino acid essential in producing L-DOPA, which is further converted into dopamine, norepinephrine, and epinephrine



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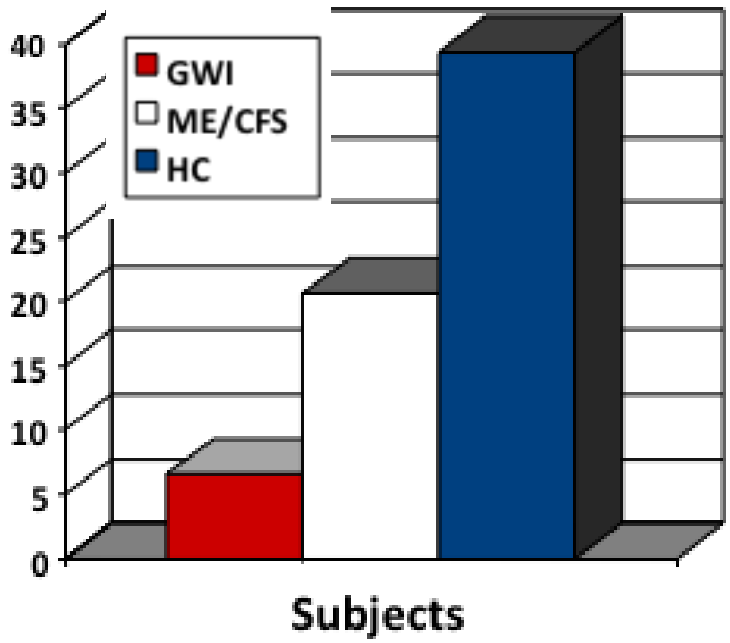
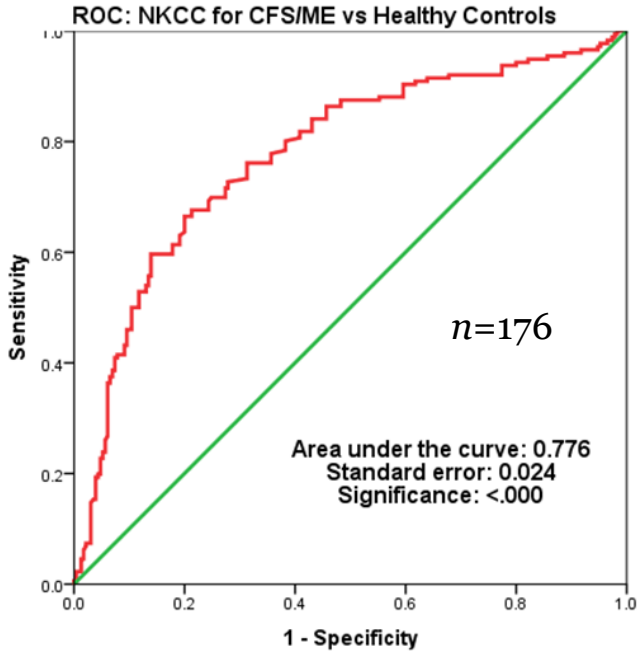
Changes in function





- NK cell cytotoxicity significantly depressed in CFS/ME (also in GWI)
- Offers a credible mechanistic biomarker

Fletcher MA, et al. (2010) Biomarkers in Chronic Fatigue Syndrome: Evaluation of Natural Killer Cell Function and Dipeptidyl Peptidase IV/CD26. PLoS ONE 5(5): e10817. doi:10.1371/journal.pone.0010817

Treatable: Targeting B cells

OPEN ACCESS Freely available online

PLoS one

Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study

Øystein Fluge[1]*, Ove Bruland[1,2], Kristin Risa[1], Anette Storstein[3], Einar K. Kristoffersen[4], Dipak Sapkota[1], Halvor Næss[3], Olav Dahl[1,5], Harald Nyland[3], Olav Mella[1,5]

1 Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway, 2 Department of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway, 3 Department of Neurology, Haukeland University Hospital, Bergen, Norway, 4 Department of Immunology and Transfusion Medicine, Haukeland University Hospital, and The Gade Institute, University of Bergen, Bergen, Norway, 5 Institute of Internal Medicine, Section of Oncology, University of Bergen, Bergen, Norway

(2011)

- Double-blind, placebo-controlled phase II study: n=30 ME/CFS
- Randomised Rituximab 500 mg/m2 or saline, twice two weeks apart, 12-month follow-up
- Reduced fatigue in 10 of 15 patients (67%) with Rituximab vs. 2 of 15 patients (13%) with placebo (p = 0.003).

Treatable: Targeting NK function

OPEN ACCESS Freely available online

PLoS one

A Double-Blind, Placebo-Controlled, Randomized, Clinical Trial of the TLR-3 Agonist Rintatolimod in Severe Cases of Chronic Fatigue Syndrome

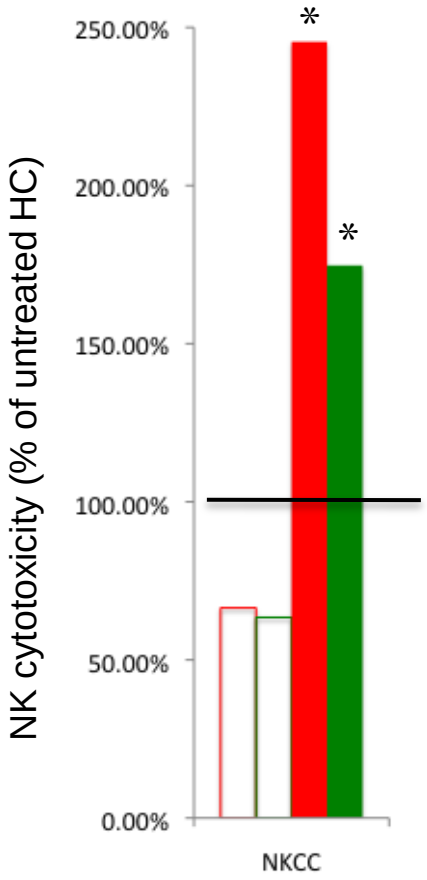
David R. Strayer[1]*, William A. Carter[1], Bruce C. Stouch[2], Staci R. Stevens[3], Lucinda Bateman[4], Paul J. Cimoch[5], Charles W. Lapp[6], Daniel L. Peterson[7], the Chronic Fatigue Syndrome AMP-516 Study Group[¶], William M. Mitchell[8]*

1 Hemispherx Biopharma, Inc., Philadelphia, Pennsylvania, United States of America, 2 BCS Consulting, Philadelphia, Pennsylvania, United States of America, 3 University of the Pacific, Stockton, California, United States of America, 4 Fatigue Consultation Clinic, Salt Lake City, Utah, United States of America, 5 Center for Special Immunology, Fountain Valley, California, United States of America, 6 Hunter-Hopkins Center, Charlotte, North Carolina, United States of America, 7 Sierra Internal Medicine Associates, Incline Village, Nevada, United States of America, 8 Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America

(2012)

- Phase III multi-center (12), double-blind, placebo controlled: n=117 ME/CFS patients
- Exercise tolerance (time to max exertion) as primary endpoint
- Randomised to 200 mg IV Rintatolimod or saline twice weekly,
- Improved exercise tolerance (>25%) 1.9 X more frequent.

Treatable: More to come



Targeting NK cells with cytokines:

- Exogenous IL-15 produces significant recovery of *in vitro* NK cell cytotoxicity and CD26 expression in ME/CFS and GWI
- Preliminary evidence for restoration of cytokine signaling patterns
- Preparing preclinical and Phase I/ II proposals for US Gov. funding agencies

Fundable: A Recognised Public Health Issue

ME/CFS research awards since 1998 :

- Office of Research on Women's Health (ORWH)
- National Institute of Allergy and Infectious Diseases (NIAID),
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS),
- National Institute for Diabetes and Digestive Diseases (NIDDK)
- National Institute of Neurological Disorders and Stroke (NINDS)

In 2011 the US DoD added ME/ CFS as a fundable topic to its Peer Reviewed Medical Research Program; $750,000 over 3 yrs

Awarded extension NIH R01 (Katz, Jason, Stewart and Broderick)

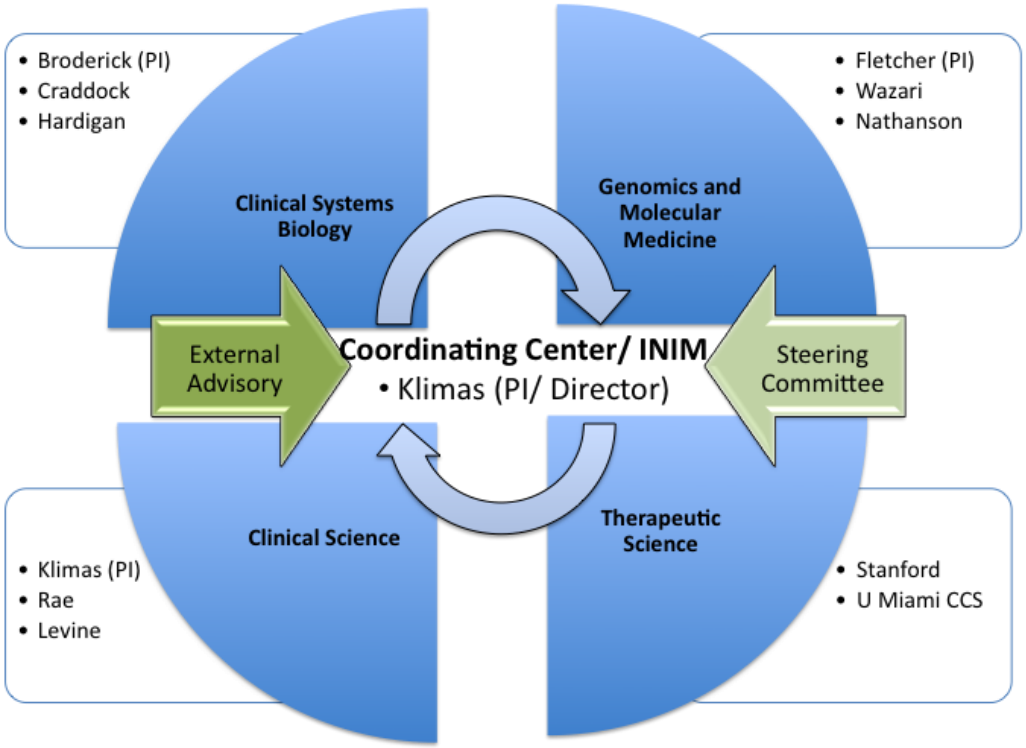
Moving forward

Evidence is supporting the view that using blood-borne markers:

- We can diagnose based on immune signaling and function
- We can screen based on immune and endocrine panels
- Avenues for early intervention that could lead to lasting results

Tools/ protocols becoming available to empower PHAC surveillance of this illness and its evolution (longitudinal study)

Critical Mass: Integrated across disciplines



- Focused effort building on strengths of 8 institutions (>$10 M)
- *Integrating* computer and experimental models with *in vitro* testing to design clinical treatment trials

Sponsorship

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